MOLECULAR CELL BIOLOGY

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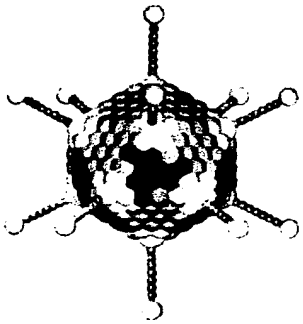

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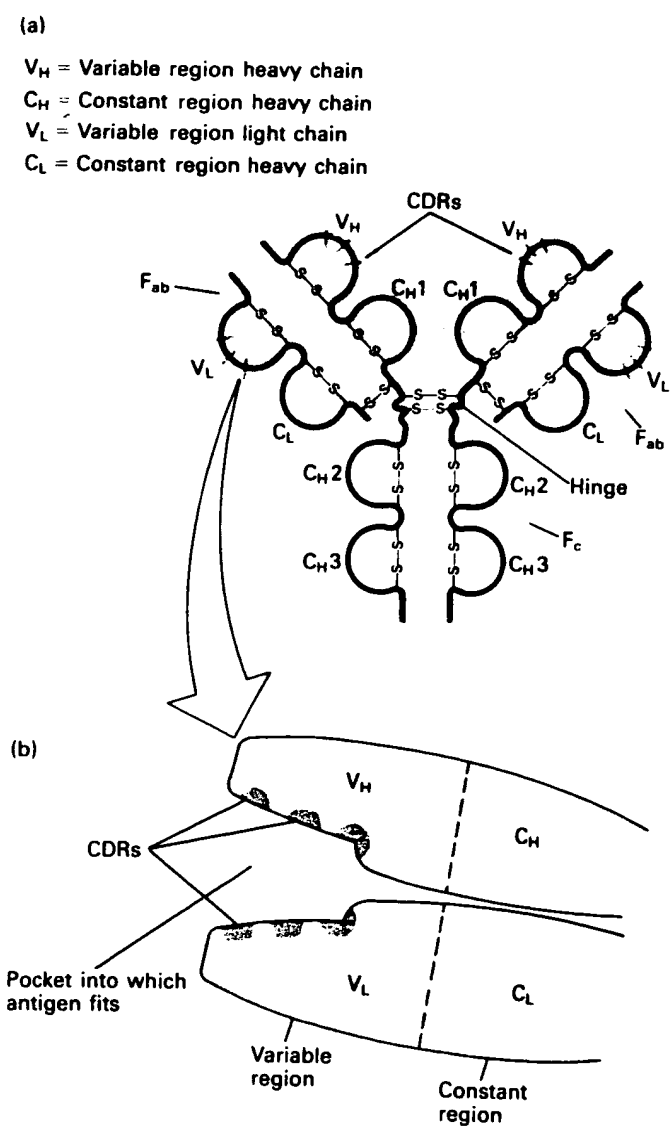
making a total of eight types of immunoglobulin. Attached to all the H chains are asparagine-linked carbohydrate chains.

Every individual antibody molecule has one type of L chain and one type of H chain. The chains are held together by disulfide bonds to form a monomer, and two monomers are linked by disulfide bonds to form the basic dimeric structure of the molecule (Figure 24-15). Within each chain, units made of about 110 amino acids fold up to form compact *domains*. Each domain has a single internal disulfide bond which holds it together. An L chain has two domains, H chains have four or five domains. The first two N-terminal domains of the H chains interact with the two L-chain domains, producing a compact unit that acts as the binding region of the antibody. In most H chains, a *hinge* region consisting of a small number of amino acids is found after the first two domains. The hinge is flexible and allows the binding regions to move freely relative to the rest of the molecule. At the hinge region are located the cysteine residues whose SH groups are linked to form the —S—S— bridges between the two monomer units of the antibody dimer. The hinge regions are the places most susceptible on the molecule to the action of protease; light protease treatment can split an antibody into two pieces, called F_{ab} and F_c fragments. The F_{ab} portion has the antigen-binding site, the F_c portion has the effector regions (see Figure 24-15).

The very first amino acid sequences determined on L chains from human myelomas made it clear that the N-terminal domain has a very variable structure while the C-terminal domain has a quite constant structure. The N-terminal domain is called the *variable region* and the C-terminal domain is called the *constant region* (Figure 24-15). H-chain sequences show the same division: within each class the N-terminal domain is highly variable and the C-terminal domains have a constant sequence. The variable domains of L and H chains are bound to one another. In fact, they interact closely to form a single compact unit (Figure 24-15). This unit is the antibody-binding site, the region of the antibody molecule that binds to antigen. This can be demonstrated by the use of an antigen that contains a reactive chemical group: the reactive group on the antigen will form a covalent bond to the variable domain of the H or L chain, showing that the variable domains form the antigen-binding pocket.



Domain structure and the complementarity-determining regions (CDRs) of an antibody. (a) The molecule is organized in disulfide bonded 110 amino acid domains, four in the heavy chain and two in the light chain. The farthest N-terminal domain of each chain is variable in sequence (V region): the other domains are constant in sequence (regions C_H1, C_H2, and C_H3 in the heavy chain and C_L in the light chain). When the molecule is protease-digested, cutting of the hinge region connecting C_H1 and C_H2, the most sensitive spot on the molecule, splits the molecule into two parts, F_{ab} (the antigen-binding domain) and F_c (the effector region). Within the V regions are segments of highly variable sequence constituting the CDRs, the amino acids that actually contact the antigen. (b) Antibody binding site. By the coordinate effort of the CDRs from light and heavy chains, a binding pocket is formed into which a specific antigen fits.